Part III: Detailed Office Action

Restriction Requirement:

Applicant's election without traverse of Claims 1-12 as drawn to non-covalent linkage of a β subunit to an α-β fusion protein, with an election of species wherein β_1 and β_2 are both FSH agonists in Paper No. 8 and 12 is acknowledged. Applicants have identified claims 1, 2, 5, 6 and 10-12 as corresponding to the elected species. The Examiner further finds that claim 3 is generic to the elected species. Accordingly, claims 1-3, 5, 6, and 10-12 are under consideration.

Formal Matters:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim 1 is objected to because of the following informalities: The claim encompasses multiple patentably distinct inventions, namely the non-elected invention, wherein there is a covalent linkage. The claim should be amended to remove the non-elected invention. Appropriate correction is required.

Claims 6 and 10-12 are objected to for encompassing non-elected species, there being no allowable generic claim. If allowability of the elected species is determined and the genus remains non-allowable, applicants will be required to amend the claims to limit to the elected species.

Note with respect to claim interpretation: Claim 1 states that β^1 and β^2 confer a "different activity on said composition". Given that applicants have elected a species wherein both β^1 and β^2 are FSH agonists, the Examiner is interpreting "different activity" to indicate *any* difference in activity, including different binding affinity for receptor, or different half-lives.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite for reciting that β^1 and β^2 correspond to different native β subunits; it is not clear whether applicants intend that β^1 and β^2 are FSH subunits from different species of animal, or alternatively whether they are allelic variants, and in either case, whether they are in their 'native' state, or could be "a variant thereof", given that the specification does not breath life and meaning into the term "correspond".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 6 and 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions in which β^1 and β^2 are from the same vertebrate species and compositions in which β^1 and β^2 are from different glycoprotein hormones, does not reasonably provide enablement for (a) compositions in which β^1 and β^2 are from different vertebrate species, or (b) wherein β^1 and β^2 are from the same glycoprotein hormone, e.g. both FSH agonists, both FSH antagonists, or an FSH agonist and an FSH antagonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With respect to item (a):

The specification does not enable species wherein β^1 and β^2 are subunits from different vertebrate species. Given that one reasonable interpretation of claim 2 is that β^1 and β^2 are from different species, the specification has not taught why one would desire to administer to one vertebrate species a β subunit from another species. The person of ordinary skill in the art would

recognize that such carries a risk of immunological reaction to such a subunit, and would not recognize such as being routine in the art. Accordingly, with respect to the claims as they read upon such species, the specification does not teach how to use the claimed invention.

With respect to item (b):

The specification discloses at page 4 that administration of the non-covalently linked β subunit having a SHORTER half-life from the covalently linked subunit allows greater activity during the half-life of the non-covalently linked β, however "the activity would decrease after the shorter half-life of the non-tethered FSHβ subunit ends." Applicants assertion is not supported by any data or working examples of such, and the Examiner finds that sound scientific reasoning would not lead to this conclusion. Accordingly, the specification does not teach how to make and use the invention with respect to complexes in which β^1 and β^2 have the same activity, including wherein they are both FSH agonists.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is methods of using noncovalently linked complexes of a single β subunit with an α-β single chain fusion protein , α and β both being the respective subunits of glycoprotein hormones. The specification discloses, and prior art confirms (see art rejections, below), that when β^1 and β^2 are subunits from different glycoprotein hormones, that the noncovalently linked complex will demonstrate activities of both hormones, e.g. will have both FSH and CG activity, if those are the β subunits used. However, there is no measure of such activity as compared to either hormone individually. It is not predictable that a single complex of a single chain α-β fusion with a non-covalently linked β subunit can demonstrate both activities simultaneously, and scientific reasoning would not lead to the conclusion that it can. This is because the single α

subunit is not bilaterally symetrical or known to have any other conformation that would be expected to accomadate two β subunits at the same time. In fact, the art teaches that the α and β subunits are intertwined in a manner that would not seem to accomadate simultaneous interaction of the α subunit with two β subunits, as would be necessary for the claimed method to accomplish a higher activity level than if only a heterodimer were administered; see for example Lapthorn et al., Nature 369:455 and Patel, Nature 369:438, both references cited by applicants . There are no reports in the prior art indicating that a single α subunit can bind to more than one β subunit at one time. Therefore, while a complex having two β subunits with *different* activities would be expected to demonstrate both those activities, it would not be expected to be at a level greater than that obtained from a single α-β heterodimer. Simply put, it would have two different activities, but each would be at a lower level than obtained from the corresponding heterodimer. Given this, if the two β subunits have the *same* activity, it stands to reason that the single α can associate with only one of them at a time. Accordingly, the skilled artisan would *not* expect that the claimed species, wherein both β^1 and β^2 are FSH agonists would, as asserted, have a "higher" activity until the subunit with the shorter half-life dissociated. What the skilled artisan would reasonably expect is that the complex would not have an activity significantly different from that of a heterodimer consisting of a single α and a single β subunit. Given such, the specification has not taught why it would be desirable to practice the claimed methods as they are drawn to species in which both β^1 and β^2 have similar activity, i.e. are from the same glycoprotein hormone, and are either both agonists or both antagonists, i.e. has not provided adequate guidance as to how to practice the claimed invention. There are no working examples demonstrating the properties of such complexes. The specification has further provided no logic or motivation for practicing the invention wherein β^1 and β^2 are agonist and antagonist, respectively, of the same glycoprotein hormone (or vice versa). Accordingly, the specification has not taught how to use the claimed methods in a manner commensurate in scope with the claims.

Rejections over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over L. Seethalakshmi et al., Journal of Urology 144:1489-1492, 1990 in view of R.K. Hyde et al., Biology of Reproduction 54(Suppl. 1) :105, Abstract 193, 1996 and D. Ben-Menahem et al., Abstract OR28-3 presented at Endo 98, Endocrine Society, 1998.

Seethalakshmi et al. teach that coadministration of hCG and FSH reverses the toxic effects of cyclosporine on male reproduction (see title). At page 1492 they conclude that administration of the two hormones "may have significant clinical implication in protecting the kidney from the nephrotoxic effects of CsA, in addition to their implications for the maintenance of normal reproductive function in CsA-treated animals."

Seethalakshmi et al. do not teach or suggest administering the FSH and hCG by administering a single chain α-β fusion protein with an additional non-covalently linked β subunit.

Hyde et al. teach that coadministration of hCGβα and FSHβ results both hCG and FSH activity. Ben-Menahem et al. teach that coadministration of FSHβα and hCGβ results in both hCG and FSH activity.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of Seethalakshmi et al. by substituting either the coadministration

of hCGβα and FSHβ as taught by Hyde et al. or the coadministration of FSHβα and hCGβ as taught by Ben-Menahem et al. One of ordinary skill in the art would have been motivated to do so to obtain the known an expected properties of having both FSH and CG activity, and would have expected success because of the teachings of both Hyde et al. and Ben-Menahem et al. that such co-administration results in both activities. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the prior art. It is noted that FSH and CG inherently have different half-lives, thus meeting the limitation of claim 3.

Claims 1-3, 5, 6, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over G. De Rosa et al., Annales d'endocrinologie 48(6):468-472, 1987 (Abstract only) in view of R.K. Hyde et al., Biology of Reproduction 54(Suppl. 1) :105, Abstract 193, 1996 and D. Ben-Menahem et al., Abstract OR28-3 presented at Endo 98, Endocrine Society, 1998.

De Rosa et al. report that administration of human menopausal gonadotropins (hMG) was effective in inducing testicular descent in 10 of 20 cases of undescended testes. The Examiner notes that hMG is comprised of FSH and LH. While the treatment was not directly for fertility, it is noted that males with undescended testes are largely infertile, thus the treatment would inherently increase fertility in the patients.

De Rosa et al. do not teach or suggest administering the FSH and LH by administering a single chain α-β fusion protein with an additional non-covalently linked β subunit.

The teachings of Hyde et al. and Ben-Menahem et al. are summarized above.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of De Rosa et al. by substituting either the coadministration of either LHβα and FSHβ or the coadministration of FSHβα and Lhβ, in view of the teachings of Hyde et al. and Ben-Menahem et al. that co-administration of a single-chain glycoprotein hormone fusion protein with an additional β subunit is effective for producing both activities in the treated patient. One of ordinary skill in the art would have been motivated to do so to obtain the known an expected properties of having both FSH and LH activity as taught by De Rosa et al., and would

have expected success because of the teachings of both Hyde et al. and Ben-Menahem et al. that such co-administration results in both activities. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the prior art. It is noted that FSH and LH inherently have different half-lives, thus meeting the limitation of claim 3.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.

Lorraine Spector, Ph.D.
Primary Examiner

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